Background on Gadolinium

What is Gadolinium?

Gadolinium is a Rare Earth Element (REE) with paramagnetic properties. On the Periodic Table its symbol is Gd and its atomic number is 64.[1,2] Gadolinium is one of 15 metallic chemical elements known as the Lanthanide Series. Lanthanides have been referred to as "bone seekers" because they tend to deposit in bone.[3, 4] Tests have confirmed that Gadolinium deposits in bone where it can remain for many years.[5,6,7,8]

Gadolinium (Gd^{3+}) has an ionic radius very similar to that of Calcium (Ca^{2+}) which is why Gd^{3+} is so toxic in biological systems – Gd^{3+} can compete with Ca^{2+} in all biological systems that require Ca^{2+} for proper function and, in doing so, the trivalent Gd^{3+} ion binds with much higher affinity.[1]

Gadolinium is toxic to mammals and it has no known biological use in the human body.[9,10,11,12,13,14,15]

Gadolinium-Based Contrast Agents are used for MRI and MRA.

Gadolinium has several specialized uses, but we will focus on its paramagnetic properties. In the early 1980s contrast agent developers determined that Gadolinium's paramagnetic properties could be used to enhance images of abnormal tissue on Magnetic Resonance Imaging (MRI) scans.[16,17]

Since free Gadolinium is toxic, the Gadolinium ion must be chelated or bound to a ligand (molecule) before it can be used as a contrast agent. The resulting complex is a Gadolinium-Based Contrast Agent or GBCA which is injected intravenously during a contrast-enhanced MRI.[18] GBCAs are also used for contrast-enhanced Magnetic Resonance Angiography (MRA). (Note that MRI and MRA are also performed without contrast.)

The intravenously administered GBCA should move rapidly through the body and then be excreted primarily via the kidneys before the toxic Gadolinium ion and ligand can separate.[19] With normally functioning kidneys, most of the GBCA should be excreted in less than two hours after injection with the remainder being excreted over the next few days. However, impaired kidney function causes the GBCA to remain in the body for much longer periods of time which can result in the separation of the contrast agent and retention of the toxic Gadolinium ion.

In their 1984 report "*Gadolinium-DTPA as a Contrast Agent in MRI: Initial Clinical Experience in 20 Patients*", Carr et al warned that "care should obviously be taken in patients with impaired renal and/or hepatic function where high *in vivo* concentrations of Gd-DTPA may occur for prolonged periods".[20] Gd-DTPA, also known as Magnevist, was the first Gadolinium-Based Contrast Agent and it was approved by the FDA in 1988. (See Background on GBCAs for details.)

When severe skin problems first appeared in 1997 in a group of dialysis patients,[21] the connection was not made to that initial warning about the use of Gadolinium-Based Contrast Agents in renally-impaired patients. It wasn't until 2006 that retained Gadolinium from GBCAs was confirmed as the probable cause.[22,23]

When Gadolinium is retained in the body, it can have serious consequences – the most serious being an incurable and potentially life-threatening disease known as Nephrogenic Systemic Fibrosis or NSF which is thought to primarily affect patients with severely impaired kidney (renal) function. It is widely recognized by the medical community and government agencies that the toxicity of retained Gadolinium is the primary contributor to the development of NSF.

NSF was first thought to be a skin disease, but it was later learned that retained Gadolinium adversely affects all body systems by causing extensive fibrosis and calcification of connective tissue and internal organs. (See Background on NSF for details.)

Patients exposed to GBCAs are at risk of retaining Gadolinium.

The risks associated with the administration of Gadolinium-Based Contrast Agents to patients with severely impaired kidney function (eGFR <30) are well-documented and recognized by the medical community and FDA. Patients with normal kidney function are not thought to be at risk of retaining Gadolinium from GBCAs; however, published literature indicates that some Gadolinium from each dose of contrast may remain in the body of all patients exposed to GBCAs.[8, 24]

A 1991 article by Rocklage et al titled "*Metal Ion Release from Paramagnetic Chelates: What is Tolerable?"* reported that "minute amounts of chelated or unchelated metals are likely to remain in the body for an extended period and could possibly result in a toxic effect." They also said it was "unlikely that MRI contrast agents would be administered repeatedly in patients".[25] Unfortunately, many patients do have multiple MRI scans with contrast which can result in more Gadolinium remaining in the patient's body.

Researchers have estimated that approximately 1% (15 mg) of the 1.5 grams of injected Gadolinium from each dose of contrast (0.1 mmol/kg body weight) may be released from the contrast agent and deposited in the bones of GBCA exposed patients including those with normal kidney function.[26]

The long-term and cumulative effects of retained Gadolinium are unknown as are the additive effects of the double or triple doses often used for contrast MRAs.

Besides severely impaired kidney function, there are other factors that can increase the risk of retaining Gadolinium. Those risk factors include acidosis, transient acute kidney injury (AKI), recent surgery, inflammatory events, abnormal vascularity, compromised blood-brain barrier, cumulative dosage, and transmetallation.[27,28,29,30] Other than kidney impairment, researchers have found that transmetallation presents the greatest potential risk for the release of the toxic metal ion from the chelate.[25,31] Transmetallation is a potential risk for every GBCA exposed patient. (See Risk Factors for more details.)

Gadolinium can deposit in brain tissue.

MRIs with contrast are frequently performed when the brain is being imaged. The brain is protected from potentially harmful compounds in the blood by the semi-permeable Blood-Brain Barrier (BBB). The intact BBB protects the brain from damage, whereas the dysfunctioning BBB allows influx of normally excluded hydrophilic molecules into the brain tissue.[32] A brain tumor or lesion causes a

disruption or break in the BBB. That "break" gives the Gadolinium-Based Contrast Agent access to the brain – regardless of the patient's level of renal function at the time of his or her contrast procedure.

GBCA product labeling indicates that Gadolinium-Based Contrast Agents "do not cross an intact blood-brain barrier"; however, "disruption of the blood-brain barrier" or "abnormal vascularity" allows accumulation in lesions such as neoplasms (tumors), abscesses, and subacute infarcts.[33,34,35,36,37,38,39,40] That is why Gadolinium is deposited in brain tumors and brain lesions, such as those seen in Multiple Sclerosis. The abnormal brain tissue then becomes more clearly defined or enhanced on magnetic resonance (MR) images.[41] Gadolinium should not remain in the body; however, the literature indicates that Gadolinium retention has occurred.

A 1995 case report by Martinez noted persistent Gadolinium retention in an extra-axial brain stem lesion of a patient with Erdheim-Chester Disease. Gadolinium retention was confirmed by comparing precontrast and postcontrast images from two MRIs performed 23 days apart.[42] A 1989 case report of Erdheim-Chester disease reported persistent enhancement of intracerebral lesions 8 days after injection with Gd-DTPA. Chemical analysis of the biopsy specimen revealed a high concentration of Gadolinium.[43]

A 2009 study by Fulciniti et al found that a Gadolinium-containing contrast agent promoted Multiple Myeloma (MM) cell growth. Autopsies of 8 MM patients with repeated exposure to the agent found "massive amounts of Gadolinium accumulation in tissues regardless of their renal function".[44]

A 2010 study by Xia et al found insoluble deposits containing Gadolinium in 7 brain tumor biopsies from 5 patients whose eGFRs were above 53 ml/min, confirming that brain tumors alter the Blood-Brain Barrier which allows the injected GBCA to deposit in brain tissue, even in patients without severe kidney problems.[45]

A 2013 study by Kanda et al found that abnormally high signal intensity detected in two regions of the brain on unenhanced T1-weighted images was related to the number of previous Gadolinium-based contrast enhanced MRIs that had been undergone by the population of patients with normal renal function.[46]

Patients with Multiple Sclerosis (MS) routinely have MRIs with contrast to monitor disease activity and response to treatment. Gadolinium will enhance "active" MS lesions due to a breakdown in the Blood-Brain Barrier.[47] Serial contrast MRIs have shown that active lesions generally enhance for a period of 1 to 2 months on average.[48,49] The enhancing lesion evolves to a chronic T2 hyperintense lesion, which is the non-specific 'footprint' of the prior inflammatory event.[50] It has been speculated "that the initial enhancing-inflammatory lesion events in the brain, place into motion, at an early stage, the processes that ultimately lead to cerebral atrophy, and these processes may include early axonal injury".[50]

While the role of enhancing-inflammatory lesions in the development of cerebral atrophy in MS is unclear, studies have demonstrated that cerebral atrophy paralleled that of contrast enhancing lesion accumulation.[51,52] As noted by Simon, atrophy, particularly that resulting from volume loss around the third ventricle, appears to be predicted by the presence of enhancing lesions at baseline.[50] Patients without enhancing lesions at baseline showed no increment (increase) in third ventricle width, while the enhancing group showed significant increments in atrophy.[50] The enhancement is the result of deposited Gadolinium; however, the literature does not indicate whether or not Gadolinium deposition or retention leads to brain atrophy.

Retention of Gadolinium from contrast MRIs has been confirmed in a patient with MS. Results of provoked urine testing for toxic metals after administration of the chelating agent EDTA showed high

levels of Gadolinium.[53] The chelating agent can extract elements from tissue in much higher quantity than would normally be excreted in urine. Removal of Gadolinium and other metals by chelation therapy was reported to definitively improve the patient's MS symptoms.

While the presence of a brain tumor or lesion alters the Blood-Brain Barrier, there are other ways that the BBB might be crossed or temporarily altered, such as the following:

- Lack of a BBB on the Optic Nerve Head,[54,55] circumventricular organs (CVOs)[56] and Chorid Plexuses [57,58]
- Having Type II Diabetes or white matter hypersensitivity like hypertension [59]
- Diffusion into the vitreous and aqueous humors of the ocular globes, perivascular spaces, and ventricles of the brain[60]
- Diffusion into the subarachnoid[61,62,63] and subdural spaces[64]
- Effects of Electromagnetic Pulse (EMP)[65,66,67,68] and Electromagnetic Fields (EMF)[69,70,71]

Note that findings of delayed and hyperintense enhancement of Cerebrospinal Fluid (CSF) have been reported in patients with normal renal function.[62,63,72,73,74]

Here are other important facts about Gadolinium and GBCAs.

- Gadolinium is neurotoxic.[75,76,77,78] It inhibits mitochondrial function and induces oxidative stress.[79,80]
- Gadolinium-Based Contrast Agents can be nephrotoxic.[81,82,83,84,85,86,87]
- Residual Gadolinium from GBCAs has been found in bone and other tissue of study animals that did not have NSF-like skin lesions.[88,89,90,91,92]
- A 2004 study by Gibby confirmed deposition of Gadolinium in bone tissue from patients with normal renal function 4 days after exposure to a GBCA.[93]
- A 2008 study by Abraham et al presented findings that indicate deposited Gadolinium (Gd) may be mobilized over time from bone stores. – "regardless of renal function at present".[94]
- A 2009 study by Darrah et al found Gadolinium in hip bone removed from a patient 8 years after her last contrast MRI, confirming Gadolinium deposits in bone where it can remain for many years.[8]
- A 2011 Mayo Clinic Study by Christensen et al found detectable concentrations of Gadolinium in fresh tissue specimens taken from two control subjects with normal renal function. Both patients had previous GBCA exposure, one 8 months and the other 16 months before their biopsy.[95]
- The release of Gadolinium from all linear Gd^{3+} complexes in human serum from *healthy* volunteers was several orders of magnitude greater than predicted by conditional stability constants.[96]
- Studies have shown that GBCAs affect blood and tissue of subjects with normal kidney function.[97,98,99,100,101,102]

- All GBCAs and Gadolinium Chloride ($GdCl^{3+}$) have been found to stimulate fibroblast proliferation in tissue taken from *healthy* subjects. (Fibroblasts play a role in the production of connective tissue and fibrosis.) [99,103,104]
- Macrocyclic agents are thought to be more stable and thereby safer to use; however, even they have been found to deposit in tissue.[88,105,106] There are now confirmed cases of NSF caused by macrocyclic agents as well.[107,108]
- Retained Gadolinium affects more than the skin. Autopsies of deceased NSF patients have found extensive multiorgan fibrosis and calcification, as well as vascular and extracellular deposits of Gadolinium.[109]

  Areas affected include: liver, lungs, intestinal wall (ileum), kidney, lymph node, skeletal muscle, diaphragm, mitral valve, aortic arch, great vessels of the heart, cardiac conduction system, left ventricle and septum, blood vessels, atrial myocardium, lesser pelvis, testes, adrenal glands, pancreas, colon, thyroid, gastrointestinal tract including esophagus and stomach, eye, brain parenchyma, subarachnoid space, dura mater including that surrounding the spinal cord.[110,111,112,113,114,115,116,117,118,119,120,121]
- Patients with normal kidney function are excreting levels of Gadolinium that are well above Mayo Laboratories Reference Range (>0.4 mcg/specimen) as long as several years after their last contrast-enhanced MRI or MRA. (See Self-Study of Retained Gadolinium and Appendix 1 of Symptom Survey Report.)
- Results of our Symptom Survey Report show high levels of commonality in participants' chronic symptoms of Gadolinium Toxicity. The symptoms are similar to those of NSF patients (See Appendix 2 of Symptom Survey Report.)

The FDA and medical industry directly involved with NSF and GBCAs are aware of these facts. However, clinicians have been told that patients with normal kidney function do not retain Gadolinium and are therefore not at risk from a contrast-enhanced MRI or MRA. Because of that, Gadolinium-related health problems may be greatly underreported.

Editorial comment:

Note the various findings in patients with normal kidney function mentioned throughout this Background on Gadolinium. It would seem that these findings might explain why patients with normal kidney function (meaning eGFR >60) are presenting clinically with various symptoms of Gadolinium Toxicity after a contrast MRI or MRA. The severity of each patient's symptoms likely depends on the total amount of Gadolinium that he or she retained from the intravenously administered Gadolinium-based Contrast Agent.

NSF may be the most severe manifestation of Gadolinium Toxicity, but there is no logical reason to think it is the only one. We believe that Gadolinium Toxicity is a "disease of degrees", all of which are potentially serious and life-changing.

Have you been affected by retained Gadolinium from a contrast MRI?

Anyone who has unexplained symptoms that you believe were caused by retained Gadolinium from a contrast MRI or MRA should report it to the FDA by filing a MedWatch Adverse Event Report. Call 1-

800-FDA-1088 or report via the FDA website at
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

When filing a report online, remember that Gadolinium-Based Contrast Agents are considered prescription medications or drugs.

It is important that Adverse Event Reports related to Gadolinium-Based Contrast Agents are filed with the FDA or the full scope of Gadolinium-related health problems may never be brought to light.

Patients outside the U.S. report to their country's equivalent governing agency.

---

[1] Sherry, A. D., Caravan, P., & Lenkinski, R. E. (2009). Primer on gadolinium chemistry. *Journal of Magnetic Resonance Imaging : JMRI*, *30*(6), 1240–8. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2853020&tool=pmcentrez&rendertype=abstract

[2] Gadolinium - Wikipedia, the free encyclopedia. (n.d.). Retrieved January 19, 2013, from http://en.wikipedia.org/wiki/Gadolinium

[3] MacDonald, N. S., & et al. (1951). The Skeletal Deposition of Yttrium. *Journal of Biological Chemisgtr*. Retrieved from http://www.jbc.org/content/195/2/837.full.pdf

[4] Johannsson, O., Perrault, G., Savoie, L., & Tuchweber, B. (1968). Action of various metallic chlorides on calcaemia and phosphataemia. *British Journal of Pharmacology and Chemotherapy*, *33*(1), 91–7. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1570281&tool=pmcentrez&rendertype=abstract

[5] Kindberg, G. M., Uran, S., Friisk, G., Martinsen, I., & Skotland, T. (2010). The fate of Gd and chelate following intravenous injection of gadodiamide in rats. *European radiology*, *20*(7), 1636–43. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882048/

[6] Gibby, W. A., Gibby, K. A., & Gibby, W. A. (2004). Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. *Investigative Radiology*, *39*(3), 138–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15076005

[7] White, G. W., Gibby, W. A., & Tweedle, M. F. (2006). Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Investigative Radiology*, *41*(3), 272–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16481910

[8] Darrah, T. H., Prutsman-Pfeiffer, J. J., Poreda, R. J., Ellen Campbell, M., Hauschka, P. V, & Hannigan, R. E. (2009). Incorporation of excess gadolinium into human bone from medical contrast agents. *Metallomics : integrated biometal science*, *1*(6), 479–88. Retrieved from http://pubs.rsc.org/en/content/articlehtml/2009/mt/b905145g

[9] HALEY, T. J., RAYMOND, K., KOMESU, N., & UPHAM, H. C. (1961). Toxicological and pharmacological effects of gadolinium and samarium chlorides. *British Journal of Pharmacology and Chemotherapy*, *17*, 526–32. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1482085/?tool=pmcentrez&rendertype=abstract

[10] Spencer, A. J., Wilson, S. A., Batchelor, J., Reid, A., Pees, J., & Harpur, E. (1997). Gadolinium Chloride Toxicity in the Rat . *Toxicologic Pathology* , *25* (3), 245–255. doi:10.1177/019262339702500301 http://tpx.sagepub.com/content/25/3/245

[11] Rees, J., Spencer, A., Wilson, S., Reid, A., & Harpur, E. (1997). Time Course of Stomach Mineralization, Plasma, and Urinary Changes After a Single Intravenous Administration of Gadolinium(III) Chloride in the Male Rat . *Toxicologic Pathology* , *25* (6), 582–589. doi:10.1177/019262339702500607 http://tpx.sagepub.com/content/25/6/582.abstract

[12] Hirano, S., & Suzuki, K. T. (1996). Exposure, metabolism, and toxicity of rare earths and related compounds. *Environmental health perspectives*, *104 Suppl* , 85–95. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1469566&tool=pmcentrez&rendertype=abstract

[13] Vassallo, D., & et al. (2011). Toxic effects of mercury, lead and gadolinium on vascular reactivity. *Braz J Med Biol Res*, *44*, 939–946. Retrieved from http://www.scielo.br/pdf/bjmbr/v44n9/1088.pdf

[14] Husztik, E., Lázár, G., & Párducz, A. (1980). Electron microscopic study of Kupffer-cell phagocytosis blockade induced by gadolinium chloride. *British Journal of Experimental Pathology*, *61*(6), 624–30. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2041618&tool=pmcentrez&rendertype=abstract

[15] Mizgerd, J., & et al. (1996). Gadolinium induces macrophage apoptosis. *Journal of Leukocyte Biology*, *59*(February), 189–195. Retrieved from http://www.jleukbio.org/content/59/2/189.full.pdf

[16] Weinmann, H.-J., Brasch, R. C., Press, W.-R., & Wesbey, G. (1984). Characteristics of Gadolinium-DTPA Complex: A Potential NMR Contrast Agent. *AJR. American ournal of roentgenology*, *March*(142), 619–624. Retrieved from http://www.ajronline.org/content/142/3/619.full.pdf

[17] Brasch, R. C. (1985). Inherent contrast in magnetic resonance imaging and the potential for contrast enhancement. The 1984 L. Henry Garland lecture. *The Western Journal of Medicine*, *142*(6), 847–53. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1306213&tool=pmcentrez&rendertype=abstract

[18] Mann, J. S. (1993). Stability of gadolinium complexes in vitro and in vivo. *Journal of Computer Assisted Tomography*, *17 Suppl 1*, S19–23. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8486827

[19] Rofsky, N. M., Sherry, A. D., & Lenkinski, R. E. (2008). Nephrogenic systemic fibrosis: a chemical perspective. *Radiology*, *247*(3), 608–12. Retrieved from http://radiology.rsna.org/content/247/3/608.full

[20] Carr, D., & et al. (1984). Gadolinium-DTPA as a Contrast Agent in MRI: Initial Clinical Experience in 20 patients. *AJR*, *August*(143), 215–224. Retrieved from http://www.ajronline.org/content/143/2/215.full.pdf

[21] Cowper, S. E., Robin, H. S., Steinberg, S. M., Su, L. D., Gupta, S., & LeBoit, P. E. (2000). Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet*, *356*(9234), 1000–1. doi:10.1016/S0140-6736(00)02694-5 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11041404

[22] Grobner, T. (2006). Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrology, dialysis, transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *21*(4), 1104–8. Retrieved from http://ndt.oxfordjournals.org

[23] Marckmann, P., Skov, L., Rossen, K., Dupont, A., Damholt, M. B., Heaf, J. G., & Thomsen, H. S. (2006). Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *Journal of the American Society of Nephrology : JASN*, *17*(9), 2359–62. doi:10.1681/ASN.2006060601 Retrieved from http://jasn.asnjournals.org/content/17/9/2359.full.pdf

[24] Abraham, J. L. (2011). Author Interview Jerrold L. Abraham, MD - Multiorgan Gadolinium Deposition and Fibrosis in a patient with Nephrogenic Systemic Fibrosis - an autopsy-based review. *Hemodialysis.com*. Retrieved August 15, 2012, from http://www.hemodialysis.com/author_interview_gd_deposition_in_pt_with_nsf.html

[25] Rocklage, S. M., Worah, D., & Kim, S.-H. (1991). Metal ion release from paramagnetic chelates: What is tolerable? *Magnetic Resonance in Medicine*, *22*(2), 216–221. doi:10.1002/mrm.1910220211

[26] SUNY. (2012). Case 10 | Particle Analysis | SUNY Upstate Medical University. Retrieved September 30, 2012, from http://www.upstate.edu/pathenvi/studies/cases/case10.php

[27] Rofsky, N. M., Sherry, A. D., & Lenkinski, R. E. (2008). Nephrogenic systemic fibrosis: a chemical perspective. *Radiology*, *247*(3), 608–12. Retrieved from http://radiology.rsna.org/content/247/3/608.full

[28] Sadowski, E. A., Bennett, L. K., Chan, M. R., Wentland, A. L., Garrett, A. L., Garrett, R. W., & Djamali, A. (2007). Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology*, *243*(1), 148–57. Retrieved from http://radiology.rsna.org/content/243/1/148.full

[29] Swaminathan, S., & Shah, S. V. (2007). New Insights into Nephrogenic Systemic Fibrosis. *Journal of the American Society of Nephrology* , *18* (10), 2636–2643. doi:10.1681/ASN.2007060645. Retrieved from http://jasn.asnjournals.org/content/18/10/2636.full.pdf+html

[30] Greenberg, S. A. (2010). Zinc transmetallation and gadolinium retention after MR imaging: case report. *Radiology*, *257*(3), 670–3. Retrieved from http://radiology.rsna.org/content/257/3/670.full

[31] Cacheris, W. P., Quay, S. C., & Rocklage, S. M. (1990). The relationship between thermodynamics and the toxicity of gadolinium complexes. *Magnetic Resonance Imaging*, *8*(4), 467–481. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2118207

[32] Salford, L. G., Nittby, H., & Persson, B. R. R. (2012). *Effects of Electromagnetic Fields from Wireless Communication upon the Blood-Brain Barrier. BioInitiative Working Group* (pp. 1–52, Section 10).Retrieved from http://www.bioinitiative.org/report/wp-content/uploads/pdfs/sec10_2012_Effects_Electromagnetic_Fields_Wireless_Communication.pdf

[33] Bayer HealthCare Pharmaceuticals. (2012). Magnevist Package Insert 2012.pdf. Retrieved October 14, 2012, from http://labeling.bayerhealthcare.com/html/products/pi/Magnevist_PI.pdf

[34] GE Healthcare. (2010). OMNISCAN Product Labeling. December2010. (020123s037lbl.pdf). Retrieved October 15, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020123s037lbl.pdf

[35] Mallinckrodt Inc. (2010). Optimark Product Labeling 2010. (020937s016lbl.pdf). Retrieved October 15, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020937s016lbl.pdf

[36] Bracco Diagnostics Inc. (2010). ProHance Product Labeling 2010. (020131s024lbl.pdf). Retrieved October 20, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020131s024lbl.pdf

[37] Bracco Diagnostics Inc. (2012). MultiHance Product Labeling 2012. 021357s011lbl.pdf. Retrieved October 11, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021357s011lbl.pdf

[38] DOTAREM-Product Information. (n.d.). Retrieved January 28, 2014, from https://gp2u.com.au/static/pdf/D/DOTAREM-PI.pdf

[39] Lantheus Medical Imaging. (2010). ABLAVAR Product Labeling 2010. (021711s003lbl.pdf). Retrieved October 15, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021711s003lbl.pdf

[40] Bayer HealthCare Pharmaceuticals. (2011). EOVIST Product Labeling 2011 (2011022090s005lbl.pdf). Retrieved October 15, 2012, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022090s005lbl.pdf

[41] Hesselink, J. R., Dunn, W. M., Healy, M. E., Hajek, P., Baker, L., & Brahme, F. J. (1986). Paramagnetic enhancement of cerebral lesions with gadolinium-DTPA. *Acta radiologica. Supplementum*, *369*, 558–60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2980556

[42] Martinez, R. (1995). Erdheim-Chester disease: MR of intraaxial and extraaxial brain stem lesions. *American Journal of Neuroradiology* , *16* (9), 1787–1790. Retrieved from http://www.ajnr.org/content/16/9/1787.full.pdf+html

[43] Tien, R. D., Brasch, R. C., Jackson, D. E., & Dillon, W. P. (1989). Cerebral Erdheim-Chester disease: persistent enhancement with Gd-DTPA on MR images. *Radiology*, *172*(3), 791–2. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2772189

[44] Fulciniti, M., et al, & Dana Farber Cancer Institute Harvard Medical School. (2009). Gadolinium Containig Contrast Agent Promotes Multiple Myeloma Cell Growth: Implications for Clinical Use of MRI in Myeloma (poster presentation). Retrieved from http://myeloma.org/pdfs/ASH2009_Fulciniti_1809.pdf

[45] Xia, D., Davis, R. L., Crawford, J. A., & Abraham, J. L. (2010). Gadolinium released from MR contrast agents is deposited in brain tumors: in situ demonstration using scanning electron microscopy with energy dispersive X-ray spectroscopy. Acta Radiologica (Stockholm, Sweden : 1987), 51(10), 1126–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20868305

[46] Kanda, T., Ishii, K., Kawaguchi, H., Kitajima, K., & Takenaka, D. (2013). High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing

Cumulative Dose of a Gadolinium-based Contrast Material. *Radiology*, 131669. Retrieved from http://dx.doi.org/10.1148/radiol.13131669

[47] Cotton, F., Weiner, H. L., Jolesz, F. A., & Guttmann, C. R. G. (2003). MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. *Neurology*, *60*(4), 640–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12601106

[48] Guttmann, C. R., Ahn, S. S., Hsu, L., Kikinis, R., & Jolesz, F. A. (1995). The evolution of multiple sclerosis lesions on serial MR. *American Journal of Neuroradiology*, *16*(7), 1481–1491. Retrieved from http://www.ajnr.org/content/16/7/1481.full.pdf+html

[49] Sicotte, N. L. (2011). Neuroimaging in multiple sclerosis: neurotherapeutic implications. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*, *8*(1), 54–62. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075734/

[50] Simon, J. H. (1999). From enhancing lesions to brain atrophy in relapsing MS. *Journal of neuroimmunology*, *98*(1), 7–15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10426356

[51] Richert, N. D., Howard, T., Frank, J. A., Stone, R., Ostuni, J., Ohayon, J., Bash, C., et al. (2006). Relationship between inflammatory lesions and cerebral atrophy in multiple sclerosis. *Neurology*, *66*(4), 551–6. Retrieved from http://www.neurology.org/content/66/4/551.abstract

[52] Bermel, R. A., & Bakshi, R. (2006). The measurement and clinical relevance of brain atrophy in mulitple sclerosis. *Lancet Neurol*, *5*, 158–70. doi:10.1016/S1474-4422(06)70349-0 Retrieved from http://www.via.cornell.edu/ece578/project/2012/g6/Brain_atrophy.pdf

[53] Fulgenzi, A., & et al. (2012). A case of multiple sclerosis improvement following removal of heavy metal intoxication. *Biometals*. Retrieved from http://regenera.pt/documents/pages/A case of multiple sclerosis improvement following removal of heavy metal intoxication.pdf

[54] Tso, M. O. M., Shih, C.-Y., & McLean, I. W. (1975). Is There a Blood-Brain Barrier at the Optic Nerve Head? *Archives of Ophthalmology*, *93*(9), 815–825. Retrieved from http://archopht.jamanetwork.com/article.aspx?articleid=631630

[55] Hofman, P., Hoyng, P., vanderWerf, F., Vrensen, G. F. J. M., & Schlingemann, R. O. (2001). Lack of Blood-Brain Barrier Properties in Microvessels of the Prelaminar Optic Nerve Head. *Invest. Ophthalmol. Vis. Sci.*, *42*(5), 895–901. Retrieved from http://www.iovs.org/cgi/content/abstract/42/5/895

[56] Maolood, N., & Meister, B. (2009). Protein components of the blood-brain barrier (BBB) in the brainstem area postrema-nucleus tractus solitarius region. *Journal of chemical neuroanatomy*, *37*(3), 182–95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19146948

[57] Yokel, R. (2006). Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration. *Journal of Alzheimer's Disease*, *10*, 223–253. Retrieved from http://pharmacy.mc.uky.edu/faculty/files/jad.pdf

[58] Engelhardt, B., Wolburg-Buchholz, K., & Wolburg, H. (2001). Involvement of the choroid plexus in central nervous system inflammation. *Microscopy research and technique*, *52*(1), 112–29. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11135454

[59] Starr, J. M., Wardlaw, J., Ferguson, K., MacLullich, A., Deary, I. J., & Marshall, I. (2003). Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*(1), 70–6. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1738177&tool=pmcentrez&rendertype=abstract

[60] Kanamalla, U. S., & Boyko, O. B. (2002). Gadolinium Diffusion into Orbital Vitreous and Aqueous Humor, Perivascular Space, and Ventricles in Patients with Chronic Renal Disease . *American Journal of Roentgenology* , *179* (5), 1350–1352. Retrieved from http://www.ajronline.org/content/179/5/1350.short

[61] Boyko, O. B., Kanamalla, U. S., Memisoglu, E., Kochan, J., & Schulman, G. (2001). Flair Imaging of Gadolinium Diffusion into Brain CSF and Vitreous of the Globe in Patients with Renal Disease: Proton MRS and DWI Correlation. Retrieved from http://members.asnr.org/abstracts/2001/01-O-1007-ASNR.pdf

[62] Morris, J. M., & Miller, G. M. (2007). Increased signal in the subarachnoid space on fluid-attenuated inversion recovery imaging associated with the clearance dynamics of gadolinium chelate: a potential diagnostic pitfall. *AJNR. American journal of neuroradiology*, *28*(10), 1964–7. Retrieved from http://www.ajnr.org/cgi/content/abstract/28/10/1964

[63] Mamourian, A. C., Jack Hoopes, P., & Lewis, L. D. (2000). Visualization of Intravenously Administered Contrast Material in the CSF on Fluid-AttenuatedInversion-Recovery MR Images: An In Vitro and Animal-Model Investigation . *American Journal of Neuroradiology* , *21* (1), 105–111. Retrieved from http://www.ajnr.org/content/21/1/105.abstract

[64] Kanamalla, U. S., Baker, K. B., & Boyko, O. B. (2001). Gadolinium Diffusion into Subdural Space . *American Journal of Roentgenology* , *176* (6), 1604–1605. Retrieved from http://www.ajronline.org/content/176/6/1604.short

[65] Guo, G., Wang, Q., Wang, J., Li, J., Ren, D., Zhen, L., Lin, H., et al. (2003). Effects of electromagnetic pulses on the blood-brain barrier of rats. *Environmental Electromagnetics, 2003. CEEM 2003. Proceedings. Asia-Pacific Conference on 4-7 Nov. 2003*. doi:10.1109/CEEM.2003.1282261. Retrieved from http://ieeexplore.ieee.org/xpl/login.jsp?reload=true&tp=&arnumber=1282261&url=http%253A

[66] Ding, G.-R., & et al. (2009). Effect of Electromagnetic Pulse Exposure on Brain Micro Vascular Permeability in Rats. *Biomedical and environmental sciences BES*, *22*, 265–268. Retrieved from http://www.besjournal.com/Articles/Archive/2009/No3/201110/P020111014405434865643.pdf

[67] Ding, G.-R., Qiu, L.-B., Wang, X.-W., Li, K.-C., Zhou, Y.-C., Zhou, Y., Zhang, J., et al. (2010). EMP-induced alterations of tight junction protein expression and disruption of the blood-brain barrier. *Toxicology letters*, *196*(3), 154–60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20412840

[68] Zhou, J. X., Ding, G. R., Zhang, J., Zhou, Y. C., Zhang, Y. J., & Guo, G. Z. (2013). Detrimental effect of electromagnetic pulse exposure on permeability of in vitro blood-brain-barrier model. *Biomedical and*

environmental sciences : BES, *26*(2), 128–37. doi:10.3967/0895-3988.2013.02.007. Retrieved from http://www.besjournal.com/Articles/Archive/2013/No2/201301/t20130116_76358.html

[69] Salford, L. G., Nittby, H., Brun, A., Grafström, G., Malmgren, L., Sommarin, M., Eberhardt, J., et al. (2008). The Mammalian Brain in the Electromagnetic Fields Designed by Man with Special Reference to Blood-Brain Barrier Function, Neuronal Damage and Possible Physical Mechanisms. *Progress of Theoretical Physics Supplement*, *173*(173), 283–309. Retrieved from http://ptps.oxfordjournals.org/content/173/283.full.pdf+html

[70] Nittby, H., Brun, A., Eberhardt, J., Malmgren, L., Persson, B. R. R., & Salford, L. G. (2009). Increased blood-brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. *Pathophysiology : the official journal of the International Society for Pathophysiology / ISP*, *16*(2-3), 103–12. Retrieved from http://www.pathophysiologyjournal.com/article/S0928-4680%252809%252900013-3/pdf

[71] Nittby, H., Grafström, G., Eberhardt, J. L., Malmgren, L., Brun, A., Persson, B. R. R., & Salford, L. G. (2008). Radiofrequency and extremely low-frequency electromagnetic field effects on the blood-brain barrier. *Electromagnetic biology and medicine*, *27*(2), 103–26. doi:10.1080/15368370802061995. Retrieved from http://weepinitiative.org/LINKEDDOCS/health/nittby.PDF

[72] Naul, L. G., & Finkenstaedt, M. (1997). Extensive cerebrospinal fluid enhancement with gadopentetate dimeglumine in a primitive neuroectodermal tumor. *American Journal of Neuroradiology*, *18*(9), 1709–1711. Retrieved from http://www.ajnr.org/content/18/9/1709.full.pdf+html

[73] Hamilton, B. E., & Nesbit, G. M. (2008). Delayed CSF enhancement in posterior reversible encephalopathy syndrome. *AJNR. American journal of neuroradiology*, *29*(3), 456–7. Retrieved from http://www.ajnr.org/content/29/3/456.full

[74] Levy, L. M. (2007). Exceeding the limits of the normal blood-brain barrier: quo vadis gadolinium? *AJNR. American journal of neuroradiology*, *28*(10), 1835–6. Retrieved from http://www.ajnr.org/content/28/10/1835.full

[75] Ray, D. E., & et al. (1996). Neurotoxic Effects of Gadopentetate Dimeglumine: Behavioral Disturbance and Morphology after Intracerebroventricular Injection in Rats. *AJNR. American Journal of Neuroradiology*, *February*(17), 365–373. Retrieved from http://www.ajnr.org/content/17/2/365.full.pdf

[76] Ray, D. E., Holton, J. L., Nolan, C. C., Cavanagh, J. B., & Harpur, E. S. (1998). Neurotoxic potential of gadodiamide after injection into the lateral cerebral ventricle of rats. . *American Journal of Neuroradiology* , *19* (8), 1455–1462. Retrieved from http://www.ajnr.org/content/19/8/1455.abstract

[77] Roman-Goldstein, S. M., Barnett, P. A., McCormick, C. I., Szumowski, J., Shannon, E. M., Ramsey, F. L., Mass, M., et al. (n.d.). Effects of Gd-DTPA after osmotic BBB disruption in a rodent model: toxicity and MR findings. *Journal of computer assisted tomography*, *18*(5), 731–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8089321

[78] Hui, F., & Mullins, H. (2009). Persistence of Gadolinium Contrast Enhancement in CSF: A Possible Harbinger of Gadolinium Neurotoxicity? *American Journal of Neuroradiology*, *January*(30), E1. Retrieved from http://www.ajnr.org/content/30/1/e1.full.pdf

[79] Feng, X., Xia, Q., Yuan, L., Yang, X., & Wang, K. (2010). Impaired mitochondrial function and oxidative stress in rat cortical neurons: implications for gadolinium-induced neurotoxicity. *Neurotoxicology*, *31*(4), 391–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20398695

[80] Xia, Q., Feng, X., Huang, H., Du, L., Yang, X., & Wang, K. (2011). Gadolinium-induced oxidative stress triggers endoplasmic reticulum stress in rat cortical neurons. *Journal of neurochemistry*, *117*(1), 38–47. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21198628

[81] Nyman, U., Elmstahl, B., Leander, P., Nilsson, M., Golman, K., & Almen, T. (2002). Are Gadolinium-based Contrast Media Really Safer than Iodinated Media for Digital Subtraction Angiography in Patients with Azotemia? *Radiology*, *223*(2), 311–318. Retrieved from http://radiology.rsna.org/content/223/2/311.full

[82] Heinrich, M. C., Kuhlmann, M. K., Kohlbacher, S., Scheer, M., Grgic, A., Heckmann, M. B., & Uder, M. (2007). Cytotoxicity of iodinated and gadolinium-based contrast agents in renal tubular cells at angiographic concentrations: in vitro study. *Radiology*, *242*(2), 425–34. Retrieved from http://pubs.rsna.org/doi/full/10.1148/radiol.2422060245

[83] Akgun, H., Gonlusen, G., Cartwright Jr., J., Suki, W., & Truong, L. D. (2006). Are Gadolinium-Based Contrast Media Nephrotoxic? A Renal Biopsy Study. *Arch Pathol Lab Med*. Retrieved August 15, 2012, from http://www.archivesofpathology.org/doi/pdf/10.1043/1543-2165(2006)130%5B1354%3AAGCMNA%5D2.0.CO%3B2

[84] Thomsen, H. S., & et al. (2002). Gadolinium-containing Contrast Media for Radiographic Examinations: A Position Paper. *European radiology*, (12), 2600–2605. Retrieved from http://www.rbrs.org/dbfiles/journalarticle_0179.pdf

[85] Elmståhl, B., Nyman, U., Leander, P., Chai, C.-M., Golman, K., Björk, J., & Almén, T. (2006). Gadolinium contrast media are more nephrotoxic than iodine media. The importance of osmolality in direct renal artery injections. *European Radiology*, *16*(12), 2712–20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16896701

[86] Penfield, J. G., & Reilly, R. F. (2007). What nephrologists need to know about gadolinium. *Nature Clinical Practice. Nephrology*, *3*(12), 654–68. Retrieved from http://dx.doi.org/10.1038/ncpneph0660

[87] Perazella, M. A. (2009). Current status of gadolinium toxicity in patients with kidney disease. *Clinical journal of the American Society of Nephrology : CJASN*, *4*(2), 461–9. Retrieved from http://cjasn.asnjournals.org/content/4/2/461.long

[88] Sieber, M. A., Pietsch, H., Walter, J., Haider, W., Frenzel, T., & Weinmann, H.-J. (2008). A Preclinical Study to Investigate the Development of Nephrogenic Systemic Fibrosis: A Possible Role for Gadolinium-Based Contrast Media. *Investigative Radiology*, *43*(1). Retrieved from http://journals.lww.com/investigativeradiology/Fulltext/2008/01000/A_Preclinical_Study_to_Investigate_the_Development.9.aspx

[89] Sieber, M. A., Lengsfeld, P., Frenzel, T., Golfier, S., Schmitt-Willich, H., Siegmund, F., Walter, J., et al. (2008). Preclinical investigation to compare different gadolinium-based contrast agents regarding their propensity to release gadolinium in vivo and to trigger nephrogenic systemic fibrosis-like lesions. *European Radiology*, *18*(10), 2164–73. Retrieved from http://www.springerlink.com/content/1615m2x5700806k4/

[90] Pietsch, H., Pering, C., Lengsfeld, P., Walter, J., Steger-Hartmann, T., Golfier, S., Frenzel, T., et al. (2009). Evaluating the role of zinc in the occurrence of fibrosis of the skin: a preclinical study. *Journal of magnetic resonance imaging : JMRI*, *30*(2), 374–83. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19629978

[91] Haylor, J., Dencausse, A., Vickers, M., Nutter, F., Jestin, G., Slater, D., Idee, J.-M., et al. (2010). Nephrogenic gadolinium biodistribution and skin cellularity following a single injection of Omniscan in the rat. *Investigative Radiology*, *45*(9), 507–12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20697223

[92] Haylor, J., Schroeder, J., Wagner, B., Nutter, F., Jestin, G., Idée, J.-M., & Morcos, S. (2012). Skin gadolinium following use of MR contrast agents in a rat model of nephrogenic systemic fibrosis. *Radiology*, *263*(1), 107–16. Retrieved from http://pubs.rsna.org/doi/pdf/10.1148/radiol.12110881

[93] Gibby, W. A., Gibby, K. A., & Gibby, W. A. (2004). Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. Investigative Radiology, 39(3), 138–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15076005

[94] Abraham, J. L., Thakral, C., Skov, L., Rossen, K., & Marckmann, P. (2008). Dermal inorganic gadolinium concentrations: evidence for in vivo transmetallation and long-term persistence in nephrogenic systemic fibrosis. *The British Journal of Dermatology*, *158*(2), 273–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18067485

[95] Christensen, K. N., Lee, C. U., Hanley, M. M., Leung, N., Moyer, T. P., & Pittelkow, M. R. (2011). Quantification of gadolinium in fresh skin and serum samples from patients with nephrogenic systemic fibrosis. Journal of the American Academy of Dermatology, 64(1), 91–6. doi:10.1016/j.jaad.2009.12.044

[96] Frenzel, T., Lengsfeld, P., Schirmer, H., Hütter, J., & Weinmann, H.-J. (2008). Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Investigative Radiology*, *43*(12), 817–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19002053

[97] Wermuth, P. J., Del Galdo, F., & Jiménez, S. A. (2009). Induction of the expression of profibrotic cytokines and growth factors in normal human peripheral blood monocytes by gadolinium contrast agents. *Arthritis and Rheumatism*, *60*(5), 1508–18. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2737360&tool=pmcentrez&rendertype=abstract

[98] Varani, J., DaSilva, M., Warner, R. L., Deming, M. O., Barron, A. G., Johnson, K. J., & Swartz, R. D. (2009). Effects of gadolinium-based magnetic resonance imaging contrast agents on human skin in organ culture and human skin fibroblasts. *Investigative radiology*, *44*(2), 74–81.

[99] Piera-Velazquez, S., Louneva, N., Fertala, J., Wermuth, P. J., Del Galdo, F., & Jimenez, S. A. (2010). Persistent activation of dermal fibroblasts from patients with gadolinium-associated nephrogenic systemic fibrosis. *Annals of the Rheumatic Diseases*, *69*(11), 2017–23. Retrieved from http://ard.bmj.com/cgi/content/abstract/69/11/2017

[100] Del Galdo, F., Wermuth, P. J., Addya, S., Fortina, P., & Jimenez, S. A. (2010). NFκB activation and stimulation of chemokine production in normal human macrophages by the gadolinium-based magnetic resonance contrast agent Omniscan: possible role in the pathogenesis of nephrogenic systemic fibrosis. *Annals of the Rheumatic Diseases*, *69*(11), 2024–33. Retrieved from http://ard.bmj.com/cgi/content/abstract/69/11/2024

[101] DaSilva, M., O'Brien Deming, M., Fligiel, S. E. G., Dame, M. K., Johnson, K. J., Swartz, R. D., & Varani, J. (2010). Responses of human skin in organ culture and human skin fibroblasts to a gadolinium-based MRI contrast agent: comparison of skin from patients with end-stage renal disease and skin from healthy subjects. *Investigative Radiology*, *45*(11), 733–9. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3164303&tool=pmcentrez&rendertype=abstract

[102] Bleavins, K., Perone, P., Naik, M., Rehman, M., Aslam, M. N., Dame, M. K., Meshinchi, S., et al. (2012). Stimulation of fibroblast proliferation by insoluble gadolinium salts. *Biological trace element research*, *145*(2), 257–67. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3273605&tool=pmcentrez&rendertype=abstract

[103] Bhagavathula, N., Dame, M. K., DaSilva, M., Jenkins, W., Aslam, M. N., Perone, P., & Varani, J. (2010). Fibroblast response to gadolinium: role for platelet-derived growth factor receptor. *Investigative Radiology*, *45*(12), 769–77. Retrieved from http://europepmc.org/articles/PMC3164279;jsessionid=i8I095NYY5uIueGBg1pw.22

[104] Edward, M., Quinn, J. A., Burden, A. D., Newton, B. B., & Jardine, A. G. (2010). Effect of different classes of gadolinium-based contrast agents on control and nephrogenic systemic fibrosis-derived fibroblast proliferation. *Radiology*, *256*(3), 735–43. Retrieved from http://radiology.rsna.org/content/256/3/735.full

[105] Tweedle, M. F., Wedeking, P., & Kumar, K. (1995). Biodistribution of radiolabeled, formulated gadopentetate, gadoteridol, gadoterate, and gadodiamide in mice and rats. *Investigative Radiology*, *30*(6), 372–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7490190

[106] Aime, S., & Caravan, P. (2009). Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *Journal of Magnetic Resonance Imaging*, *30*(6), 1259–1267. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2822463&tool=pmcentrez&rendertype=abstract

[107] Wollanka, H., Weidenmaier, W., & Giersig, C. (2009). NSF after Gadovist exposure: a case report and hypothesis of NSF development. *Nephrology Dialysis Transplantation* , *24* (12), 3882–3884. Retrieved from http://ndt.oxfordjournals.org/content/24/12/3882.full.pdf+html

[108] Elmholdt, T. R., Jorgensen, B., Ramsing, M., Pedersen, M., & Olesen, A. B. (2010). Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol. *NDT Plus*, *3*(3), 285–287. Retrieved from http://ckj.oxfordjournals.org/content/3/3/285.full

[109] Sanyal, S., Marckmann, P., Scherer, S., & Abraham, J. (2011). Multiorgan gadolinium (Gd) deposition and fibrosis in a patient with nephrogenic systemic fibrosis - an autopsy-based review. *Nephrology Dialysis Transplant*, (0), 1–11. Retrieved from http://ndt.oxfordjournals.org/content/early/2011/03/25/ndt.gfr085.full.pdf

[110] Ting, W. W., Stone, M. S., Madison, K. C., & Kurtz, K. (2003). Nephrogenic fibrosing dermopathy with systemic involvement. *Archives of Dermatology*, *139*(7), 903–6. Retrieved from http://archderm.jamanetwork.com/article.aspx?articleid=479394

[111] Aggarwal, A., Froehlich, A. A., Essah, P., Brinster, N., High, W. A., & Downs, R. W. (2011). Complications of nephrogenic systemic fibrosis following repeated exposure to gadolinium in a man with hypothyroidism: a case report. *Journal of Medical Case Reports*, *5*, 566. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3253728&tool=pmcentrez&rendertype=abstract

[112] Gibson, S., Farver, C., & Prayson, R. (2006). Multiorgan Involvement in Nephrogenic Fibrosing Dermopathy An Autopsy Case and Review of the Literature. Gibson SE, Farver CF, Prayson RA. Arch Pathol Lab Med. 2006;130:209–212. *Arch Pathol Lab Med*, (130), 209–212. Retrieved from http://www.archivesofpathology.org/doi/pdf/10.1043/1543-2165%282006%29130%5B209%3AMIINFD%5D2.0.CO%3B2

[113] Daram, S. R., Cortese, C. M., & Bastani, B. (2005). Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: report of a new case with literature review. *American Journal of Kidney Diseases : the official journal of the National Kidney Foundation*, *46*(4), 754–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16183432

[114] Krous, H. F., Breisch, E., Chadwick, A. E., Pinckney, L., Malicki, D. M., & Benador, N. (2007). Nephrogenic systemic fibrosis with multiorgan involvement in a teenage male after lymphoma, Ewing's sarcoma, end-stage renal disease, and hemodialysis. *Pediatric and Developmental Pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*, *10*(5), 395–402. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17929984

[115] Kucher, C., Steere, J., Elenitsas, R., Siegel, D. L., & Xu, X. (2006). Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis with diaphragmatic involvement in a patient with respiratory failure. *Journal of the American Academy of Dermatology*, *54*(2 Suppl), S31–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16427988

[116] Swaminathan, S., High, W. A., Ranville, J., Horn, T. D., Hiatt, K., Thomas, M., Brown, H. H., et al. (2008). Cardiac and vascular metal deposition with high mortality in nephrogenic systemic fibrosis. *Kidney International*, *73*(12), 1413–8. Retrieved from http://dx.doi.org/10.1038/ki.2008.76

[117] Koreishi, A., & et al. (2009). Nephrogenic Systemic Fibrosis A Pathologic Study of Autopsy Cases. *Arch Pathol Lab Med*, *133*(December), 1943–1948. Retrieved from http://www.archivesofpathology.org/doi/pdf/10.1043/1543-2165-133.12.1943

[118] Saenz, A., Mandal, R., Kradin, R., & Hedley-Whyte, E. T. (2006). Nephrogenic fibrosing dermopathy with involvement of the dura mater. *Virchows Archiv : an international journal of pathology*, *449*(3), 389–91. Retrieved from http://link.springer.com/article/10.1007%2Fs00428-006-0246-x

[119] Perez-Rodriguez, J., Lai, S., Ehst, B. D., Fine, D. M., & Bluemke, D. A. (2009). Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment--report of 33 cases. *Radiology*, *250*(2), 371–7. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2663356&tool=pmcentrez&rendertype=abstract

[120] Barker-Griffith, A., Goldberg, J., & Abraham, J. L. (2011). Ocular pathologic features and gadolinium deposition in nephrogenic systemic fibrosis. *Archives of Ophthalmology*, *129*(5), 661–3. Retrieved from http://archopht.jamanetwork.com/article.aspx?articleid=427337

[121] Jornet, A. R. et al. (2009). Revista Nefrologia - Gadolinium-induced systemic fibrosis in severe renal failure. *Revista Nefrologia*. Retrieved September 28, 2012, from http://www.revistanefrologia.com/modules.php?name=articulos&d_op=&idarticulo=129&idlangart=EN&preproduccion=